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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/930,440	08/16/2001	Michael J. Betenbaugh	PF509P2	1490

30743 7590 07/08/2004

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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 07/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/930,440	BETENBAUGH ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,48-70 and 72-243* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,48-70 and 72-243* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 48-70, 72-243 are currently pending and are present for examination (claim 71 is missing due to improper numbering).

Applicants' amendments and arguments filed on 4-23-04, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 112-126, 151-159, 185-200, 226-234 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 112-126, 151-159, 185-200, 226-234 recite the phrase "conservative variants". The metes and bounds of the above phrase is not clear to the Examiner. The above problem of clarity is compounded by the fact that applicant in some instances specifies "functional variant" (for example see claim 112) and in other instances does not. It is not clear to the Examiner as what variant the applicant is claiming in spite of definition for the "conservative variants" in the specification. Amending the claim to clearly indicate that the variants are conserve both the structure and the function would overcome the above rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 48-70, 72-96, 169-184, 217-225 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) a genetically modified cell that expresses a polynucleotide comprising a nucleotide sequence represented by SEQ ID NO:3 or a polynucleotide that hybridizes under stringent conditions to SEQ ID NO:3 or a conservative variant of the same encoding a CMP-SA synthase with an amino acid sequence SEQ ID NO:4 and a polynucleotide with SEQ ID NO:5 or a polynucleotide that hybridizes under stringent conditions to SEQ ID NO:5 or a conservative variant of the same encoding a polypeptide with SEQ ID NO:6 having SA phosphate synthase (SAS) activity, 2)being enabling for a genetically modified cell that expresses a polynucleotide encoding a CMP-SA synthase with an amino acid sequence SEQ ID NO:4 and a polynucleotide encoding a polypeptide with SEQ ID NO:6 having SA phosphate synthase (SAS) activity or a polypeptide with SEQ ID NO:8, does not reasonably provide enablement for any such recombinant or genetically modified cell that co-expresses any polynucleotide that is 90% homologous to either SEQ ID NO:3 or 5 or any polynucleotide that encodes a polypeptide that is 90% homologous to either SEQ ID NO:4, 6 or 8 from any source as claimed in above claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3)

the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1, 48-70, 72-96, 169-184, 217-225 are so broad as to encompass recombinant or genetically modified cell that co-expresses any polynucleotide that is 90% homologous to either SEQ ID NO:3 or 5 or any polynucleotide that encodes a polypeptide that is 90% homologous to either SEQ ID NO:4, 6 or 8 from any source as claimed in above claims. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides encoding CMP-SA synthase and polynucleotide encoding sialic acid phosphate synthase (SAS), broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequences SEQ ID NO:4, 6 and 8. It appears that the specification is limited to only polynucleotides encoding CMP-SA synthase and SAS but provides no guidance with regard to polynucleotides that have a nucleotide sequence that is 90% identical to SEQ ID NO:3 or 5 or polynucleotides encoding polypeptides that have an amino acid sequence that is 90% identical to SEQ ID NO:4, 6, or 8 from any or all sources and the making of variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of

experimentation required to make the claimed cell, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims.

The specification does not support the broad scope of the claims which encompasses a recombinantly made cell comprising any polynucleotide from any source encoding CMP-SA synthase and a polynucleotide encoding sialic acid phosphate synthase (SAS) as claimed in above claims because the specification does not establish: (A) a rational and predictable scheme for modifying the polynucleotides SEQ ID NO:3 or 5 in order to produce variant polynucleotides that are 90% identical to and still encode polypeptides having the above activity; (B) a rational and predictable scheme to modify the polypeptide sequences with SEQ ID NO:4, 6, or 8 such that said polypeptides continue to have CMP-SA synthase or SAS; and (B) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, making

recombinant cells having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicants submit that as a result of information obtained during the interview of March 17, 2004, it is Applicant's understanding that claims directed to above invention would be enabled. Examiner respectfully disagrees. Examiner only suggested steps applicant can pursue in order to overcome the previous enablement rejection, one of which, was to provide a set percent homology of the polynucleotide and polypeptide used to make the recombinant cells based on the support in the specification for making the same and provide arguments as to why such percent homology would be enabled. Applicants have not provided any such arguments. In view of the above, Examiner continues to maintain the enablement rejection for the above claims.

Claims 1, 48-70, 72-243 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to a cell comprising or expressing a genus of polynucleotides that have 90% sequence identity with SEQ ID NO:3, 5 (polynucleotides) or SEQ ID NO:4, 6, or 8 (polypeptides) or polynucleotides that hybridize to SEQ ID NO:3 or 5 or conservative variants of above polynucleotides/polypeptides that have not been described in the specification.

The specification does not contain any disclosure of the function of polynucleotide sequences or the polypeptide sequences are required to make the claimed genetically modified cells . The genus of polynucleotide and polypeptide sequences that comprise these above polynucleotides is a large variable genus with the potentiality of having many different functions. Therefore, many functionally unrelated DNAs and polypeptides are encompassed within the scope of these claims, including partial sequences. The specification discloses only two/three species of the claimed genus, which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Reiterating the function of the polynucleotides and the polypeptides in the claims would overcome the above rejection.

Conclusion

None of the claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 703-872-9306 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Manjunath N. Rao
July 6, 2004